



## ORIGINAL RESEARCH

# Baseline Serum Prolactin in Drug-naïve, First-episode Schizophrenia and Outcome at Five Years: Is it a Predictive Factor?

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## ABSTRACT

**Objective:** Serum prolactin is influenced by antipsychotic use but its relationships with psychopathology and general functioning are not clear. This study aimed to assess these relationships.

**Design:** Serum prolactin levels were measured in patients with schizophrenia before being treated with antipsychotics and at various follow-up points.

**Setting:** The study was conducted in a nongovernmental psychiatric treatment center in Mumbai, India.

**Participants:** The participants included 30 male and 30 female drug-naïve patients with schizophrenia and 31 control participants.

**Measurements:** The severity of psychopathology at baseline, three weeks, six weeks, and five years following treatment was assessed using a modified Brief Psychiatric Rating Scale. The Global

Assessment of Functioning questionnaire was used at baseline and five years follow up.

**Results:** Contrary to our hypotheses, prolactin levels in male but not female patients at baseline were twice those of control volunteers. Correlations between prolactin, Brief Psychiatric Rating Scale, and Global Assessment of Functioning measurements were not significant for any time point up to six weeks, but were only significant at the five-year follow-up appointments, indicating that those patients with higher levels of serum prolactin had a better outcome at five years.

**Conclusion:** Baseline serum prolactin levels in drug-naïve patients with schizophrenia may be used for long-term prognosis, but are not reliable indicators of psychopathology and prognosis in the short term. Future research is needed to conclude with confidence whether or not prolactin can be

used as a biomarker of psychopathological and overall functioning in schizophrenia.

## INTRODUCTION

Prolactin is released from the anterior pituitary and is regulated by the prolactin inhibitory factor (PIF) dopamine. The dopamine hypothesis of increased dopaminergic activity in the mesolimbic dopaminergic projections is the most widely accepted theory behind schizophrenic symptomatology and is often treated with antipsychotics.<sup>1</sup> Interestingly, elevated serum prolactin levels frequently occur in patients treated with therapeutic doses of conventional antipsychotics, which block dopamine receptors.<sup>2-4</sup> It has also been correlated with symptoms of schizophrenia.<sup>5</sup> It is likely that serum prolactin levels may also reflect the mesolimbic dopaminergic activity. On the basis of this hypothesis, it may be suggested that in drug-naïve patients with schizophrenia, an increase in dopaminergic activity and psychopathology is associated with a decrease in serum prolactin concentrations.

Various studies<sup>6-9</sup> have reported normal or lower serum prolactin levels in drug-naïve patients with acute schizophrenia and decreased prolactin levels in patients with chronic schizophrenia without ventricular dilatation. Some studies have shown an association between early relapse following neuroleptic withdrawal and low serum prolactin levels.<sup>10-12</sup> Recently, serum prolactin levels, due to antipsychotic side effects and their impact on schizophrenia, have been considered “controversial.”<sup>13</sup> It has also been shown that increased baseline prolactin levels are inversely related to severity of psychopathology at baseline in drug-naïve patients with schizophrenia.<sup>14</sup> It is possible that as dopamine activity decreases after prolonged treatment, levels of

serum prolactin diminish as well. We suggest that if an association can be established between baseline serum prolactin levels and psychopathology or level of functioning in the long term in drug-naïve patients with schizophrenia, serum prolactin levels can conceivably be used as a predictor of outcome. In order to test this hypothesis, the present study was undertaken with the following objectives:

1. To measure serum prolactin levels at baseline in drug-naïve patients with schizophrenia
2. To conduct correlations between baseline serum prolactin levels and severity of psychopathology and outcome in the short term (baseline, 3, and 6 weeks).
3. To conduct correlations between baseline serum prolactin levels and measures of psychopathology and the level of functioning in a long-term follow-up at five years.

## METHODS

**Setting.** The study was conducted in a nongovernmental psychiatric treatment center (Silver Mind Hospital [PRERANA Charitable Trust]) in Mumbai, India.

**Participants.** There were 60 consecutive patients (30 male and 30 female) included in this study who were attending the outpatient department of the hospital. Additionally, 31 healthy control participants (20 male and 11 female) provided blood samples. The 60 patients satisfied all inclusion and exclusion criteria. This sample was selected from a cohort already taking part in a 15-year outcome study of schizophrenia. Inclusion criteria were as follows: 1) subject satisfied International Classification of Disease (ICD) criteria for schizophrenia (ICD-10, WHO, 1992);<sup>15</sup> 2) subject suffering from his or her first episode of schizophrenia; 3) subject was drug-naïve (never received any antipsychotics in the past); and 4)

subject provided consent and willingness to participate in the study and follow up.

The exclusion criteria were as follows: 1) presence of any other psychiatric morbidity, such as alcohol dependence, which is likely to interfere with diagnosis and follow up; 2) presence of any concurrent medical or endocrine disorder; 3) pregnant or lactating; 4) history of full-term pregnancy in the last year; and 5) administration of other medications that are likely to alter prolactin levels.

**Procedure.** All patients were clinically examined, individually interviewed, and diagnosed by a consultant psychiatrist. The required data were then collected using specially prepared forms for the study. In order to obtain an objective history of the patients, accompanying close relatives were interviewed. For the purpose of assessing the severity of psychopathology, all patients were rated on the Brief Psychiatric Rating Scale (BPRS)<sup>16</sup> at baseline, three weeks, six weeks, and at five years follow up. Also measured was the outcome of treatment, which was assessed using the Global Assessment of Functioning (GAF)<sup>17</sup> at baseline and at the five-year follow up only.

Prior to any pharmacological treatment, 5mL of venous blood was collected to measure serum prolactin levels, which was determined by radio-immuno assay (RIA). Prolactin levels were also collected from the consenting healthy volunteers using the same assay. All patients were treated with haloperidol 15 to 45mg/day and trihexyphenidyl 6 to 12mg/day for the first six weeks and with “treatment as usual” (TAU) thereafter.

Baseline serum prolactin levels in drug-naïve male and female patients were compared with that of controls using the independent student's *t*-test. Pearson-Product-Moment correlation coefficients between baseline serum prolactin

and scores on BPRS at baseline, three weeks, six weeks, and at five years in male and female patients were obtained. Correlations between prolactin levels and GAF measures at baseline and at the five year follow up were also conducted. All results were considered significant when the probability of committing a Type-1 error was less than 0.05 ( $p < 0.05$ ).

## RESULTS

Of the original sample, 19 patients dropped out of the study. Thus, 18 men and 23 women (N=41) were available for assessment at five years. Out of those remaining, one male patient and three female patients were removed from the analysis due to abnormally high serum prolactin concentrations (more than 100ng/mL). These observed levels were possibly due to unreported neuroleptic exposure. As a result, 18 male patients and 20 female patients were included in the final analysis. The mean (SD) age of the male patients (n=18) was 31.2 ( $\pm 4.8$ ) years and female patients (n=20) was 27.3 ( $\pm 5.6$ ) years. The mean (SD) age for the male volunteers was 22.6 ( $\pm 3.8$ ), whereas the female volunteers' mean (SD) age was 21.3 ( $\pm 4.5$ ) years. There were no significant differences in age between the patients and the volunteers for either gender (male:  $t(37)=0.83$ ,  $p=ns$ , female:  $t(17)=0.21$ ,  $p=ns$ ).

The mean (SD) baseline serum prolactin concentrations in drug-naive patients with schizophrenic for male patients was 28.37ng/mL ( $\pm 11.26$ ) and was 48.31ng/mL ( $\pm 24.46$ ) for female patients. These values were two-fold higher than the values in the control male subjects (12.20ng/mL [ $\pm 5.05$ ] and female subjects (23.72ng/mL [ $\pm 7.98$ ]). The difference was statistically significant for men but not for women (for men  $t(37)=2.30$ ,  $p < 0.05$ ; for women  $t(17)=0.33$ ,  $p=ns$ ). The lack of significant difference in women was likely due

**TABLE 1.** Correlations between serum prolactin and BPRS in male subjects

Time Point	Value of $r$ (n=18)	$t$	$df$	Probability ( $p$ )
At base	0.091	0.081	17	NS
At 3 weeks	0.223	0.94	17	NS
At 6 weeks	0.098	0.098	17	NS
At 5 years	0.764	5.02	18	<0.001

**TABLE 2.** Correlations between serum prolactin and BPRS in females

Time Point	Value of $r$ (n=18)	$t$	$df$	Probability ( $p$ )
At base	0.071	0.17	6	NS
At 3 weeks	0.46	1.26	6	NS
At 6 weeks	0.5	1.41	6	NS
At 5 years	0.5	2.31	18	<0.01

**TABLE 3.** Correlations between serum prolactin levels and global assessment of functioning at five years

Time Point	Value of $r$	$t$	$df$	Probability ( $p$ )
AT BASE				
Total sample (N=38)	0.476	3.25	36	< 0.001
Males (n=18)	0.156	0.63	16	NS
Females (n=20)	0.067	0.29	18	NS
AT 5 YEARS				
Total sample (N=38)	0.629	4.85	36	<0.001
Males (n=18)	0.775	4.91	16	<0.001
Females (n=20)	0.892	8.37	19	0.001

to the small sample size.

Significant correlations were observed between prolactin measures and outcome at five years for psychopathology (BPRS) and levels of functioning (GAF) in both men and women (Tables 1, 2, and 3). There were no significant correlations between prolactin measures at baseline and BPRS (baseline, 3, or 6 weeks) or GAF (baseline) when selecting for men and women separately. At five years, however, all correlations between prolactin levels with BPRS and GAF were significant regardless of gender.

## DISCUSSION

For over 30 years, serum prolactin has been studied in a variety of psychiatric disorders, such as schizophrenia, mania, and depression.<sup>18–20</sup> The literature reports that normal or reduced serum prolactin levels in drug-naïve patients with schizophrenia are to be expected.<sup>6–9</sup> In contrast to these studies and contrary to the present hypothesis, significantly higher baseline serum prolactin levels were observed in male and female patients. The increase was statistically significant in male but not in female patients, who had slightly larger variance and a small sample size.

This increase at baseline raises a number of questions. The literature reports that serum prolactin levels depend on a number of factors, such as gender of the patient, physical and psychological stress experiences, and hypoglycemia, apart from the presence or absence of psychiatric disorders and use of psychotropic drugs.<sup>21</sup> It has also been proposed that prolactin secretion patterns differ in acute states of psychosis<sup>21</sup> where marginal or significant increases in prolactin levels may be expected due primarily to “nondopaminergic excitatory factors” of prolactin secretion.<sup>22</sup> The literature also reports that elevated serum prolactin levels have been observed

after stressful events, hypoglycemia, and neuroleptic administration.<sup>22,23</sup> It is often observed that drug-naïve patients with schizophrenia suffer their first episodes when triggered by stressful events and continue to experience stress until neuroleptics are administered to manage their psychoses. It is reasonable to assume then that increased norepinephrine and cortisol in the patient's system would mask the dopamine's ability to inhibit prolactin release. Since we did not measure cortisol or norepinephrine, we cannot comment further.

In our study, we also conducted correlational analyses between prolactin levels with BPRS and GAF measures separately. There were no significant correlations between serum prolactin levels and scores on BPRS at baseline, three, and six weeks, nor was there a significant correlation between GAF and prolactin at baseline. However, there were significant correlations between prolactin and BPRS or GAF at five years follow up. We do not have an explanation for this result other than there is the possibility that psychopathology and outcome measures are associated with the ability of patients to handle stress. It is possible that high levels of stress and, hence, increased prolactin at baseline predicts a positive outcome for this patient population. However, this result and the fact that we have a small sample size require that these data be interpreted conservatively.

In this study, we wished to provide predictive biological measures for the drug-naïve, first-episode patient with schizophrenia. Lacking in the literature and in this study are prolactin measures at all time points for BPRS and GAF measures. During the time when this study was proposed, we did not have the resources to measure at all time points but we are now considering adding this component in a future. Despite this limitation,

this study, to our knowledge, is the first that provides data relating prolactin levels to psychopathology and functioning at five years follow up. This association is not completely without precedent. There are reports that prolactin levels correlate with outcome measures, but it was not indicated to be a robust phenomenon.<sup>24,25</sup>

In conclusion, as observed in this study, serum prolactin levels cannot be reliably used in the short term as an objective indicator of psychopathology in in-patient, but tentatively can be considered for predicting long-term outcomes. Future investigations and replications in this area may provide valuable insight into predictive factors of outcome in schizophrenia

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